Polymyositis: is there anything left? A retrospective diagnostic review from a tertiary myositis centre

Jesus Loarce-Martos[1], James B. Lilleker[2,3], Matthew Parker[4], Neil McHugh[5,6], Hector Chinoy[7,8].

1. Rheumatology department, Hospital Universitario Ramón y Cajal, Madrid, Spain.
2. Centre for Musculoskeletal Research, School of Biological Sciences, Faculty of Biology, Medicine and Health, Manchester Academic Health Science Centre, University of Manchester, Manchester, United Kingdom.
3. Manchester Centre for Clinical Neuroscience, Salford Royal NHS Foundation Trust, Salford, United Kingdom.
4. Department of Rheumatology, RPA Institute of Rheumatology and Orthopaedics, Royal Prince Alfred Hospital, Sydney, NSW, Australia.
5. Department of Pharmacy and Pharmacology, University of Bath, Bath, UK.
6. Royal National Hospital for Rheumatic Disease, Bath, UK.
7. National Institute for Health Research Manchester Musculoskeletal Biomedical Research Centre, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, University of Manchester, Manchester, United Kingdom.
8. Department of Rheumatology, Salford Royal NHS Foundation Trust, Salford, United Kingdom.

Corresponding author:

Jesús Loarce-Martos

Address: Hospital universitario Ramón y Cajal, Ctra. de Colmenar Viejo km. 9,100 28034 Madrid (Spain)

E-mail: jesus.loarce@salud.madrid.org

ORCiD iD: https://orcid.org/0000-0003-1352-9539

ABSTRACT

***Objective**:* The current classification criteria for idiopathic inflammatory myopathy (IIM) retain polymyositis (PM) as a major disease subgroup. However, evolution in the understanding of IIM has suggested that many of these patients could be better described as having an alternative diagnosis. In the present study, we apply the latest understanding of IIM subtyping to retrospectively review PM diagnoses in a large cohort of IIM patients.

***Methods**:* Within a previously reported cohort of 255 patients from a UK tertiary myositis clinic, 37 patients classified as PM according to both the EULAR/ACR IIM criteria and expert opinion were identified. Clinical data and complementary tests were reviewed, and consensus decisions regarding final classification were reached in each case.

***Results**:* Nine (9/37, 24.3%) patients remained classified as PM, 3.5% (9/255) of the original cohort; these PM patients were seronegative for myositis antibodies, responsive to immunosuppression, and in 4/7 (57.1%) patients where muscle biopsy was performed had HLA-1 upregulation and endomysial inflammatory infiltrates. Immune-mediated necrotizing myopathy (5/37, 13.5%) and connective tissue disease overlap myositis (7/37, 19%) were the main alternative diagnoses. The remaining patients were diagnosed as: unspecified myopathy (6/37, 16%), dermatomyositis (2/37, 5%), cancer-associated myopathy (3/37, 8.1%), and non-inflammatory myopathy (1/37, 3%, myofibrillar myopathy). Four patients (4/37, 10%) had insufficient data available to confidently reclassify.

***Conclusion**:* Our study confirms that PM can now be considered a rare IIM subgroup. A thorough examination, complete myositis autoantibody panel, and careful interpretation of the biopsy results is recommended to confirm the correct IIM sub-type.

Keywords: polymyositis; immune-mediated necrotizing myopathy; connective tissue disease overlap myositis; idiopathic inflammatory myopathy.

KEY MESSAGES:

- Classification criteria for inflammatory myopathies do not currently include subgroups that are considered relevant.
- Polymyositis is rare and should be only considered after other disease subgroups are excluded.
- Immune-mediated necrotizing myopathy or connective tissue disease-overlap myositis should be regarded as differential diagnoses.

INTRODUCTION

Idiopathic inflammatory myopathies (IIM) are a heterogeneous group of autoimmune connective tissue diseases characterised by skeletal muscle inflammation and weakness, often accompanied by involvement of other systems including the skin, lung, or joints. The identification of specific IIM sub-types allows clinicians to predict prognosis, make individualised treatment plans, and facilitate development of targeted therapeutic approaches.

The understanding of polymyositis (PM) has evolved substantially since the Bohan and Peter criteria were published in 1975(1,2). An expanded variety of IIM subgroups are now recognised, defined according to clinical features, histopathological findings, and the presence of myositis-specific (MSA) or myositis-associated autoantibodies (MAA). Patients historically labelled with PM may now be considered to have an alternative IIM clinical sub-type, including immune-mediated necrotizing myopathy (IMNM), anti-synthetase syndrome (ASS), connective tissue-disease-overlap myositis (CTD-OM), cancer-associated myositis (CAM), or inclusion body myositis (IBM)(3).

There are several proposed criteria to distinguish the IIM sub-types, but are mainly empirically derived and not fully validated(4–8). In contrast, the recent EULAR/ACR classification criteria for IIM were developed and validated using robust procedures(9). Nevertheless, limitations remain, notably the retention of PM as a major diagnostic category and the inability to distinguish IIM subgroups such as IMNM or ASS. Consequently, diagnostic subgroups used in clinical practice are increasingly diverging from those which we are able to apply using the published criteria(10,11).

Parker *et al* previously described the performance of the EULAR/ACR criteria in our “real world” IIM cohort and examined agreement with expert opinion(10). In summary, 255 patients with definite or probable IIM by EULAR/ACR criteria were identified. 124 patients were classified as PM according to these criteria, but among those patients only 37 (39.8%) were classified as PM according to expert opinion, given that classification criteria fail to correctly diagnose some patients(12). Given the ongoing uncertainties regarding the existence of PM as a diagnostic subgroup of IIM, we undertook a detailed review of these 37 cases seeking to understand the accuracy of diagnosis and to determine the phenotypic associations in this group.

MATERIALS AND METHODS

Case identification and classification

We re-analysed data regarding a previously described cohort of adult-onset IIM cases from Salford Royal NHS Foundation Trust (SRFT), UK, focussing on those classified as PM(10). From a total of 255 IIM cases, 37 patients were identified as PM by both EULAR/ACR criteria (probable or definite) and expert opinion. Records were reviewed to confirm clinical characteristics, autoantibody (Ab) profile, electromyography (EMG), muscle magnetic resonance imaging (MRI), and muscle biopsy findings. Information about administered treatments and outcomes was also examined.

As this is a "real world" cohort, not all patients had every investigation performed. However, in most cases, antibodies were detected using the Euroimmun myositis line blot (Euroline Autoimmune Inflammatory Myopathies, Lübeck, Germany), which includes anti-Mi2, anti-Tif1 gamma, anti-MDA5, anti-NXP2, anti-SAE1, anti-Ku, anti-Pm-Scl, anti-Jo1, anti-PL7, anti-PL12, anti-EJ, anti-OJ, anti-SRP and anti-Ro-52. In addition, some patients had immunoprecipitation performed and testing for HMGCR Abs by ELISA. Antinuclear antibodies (ANA) were detected by indirect immunofluorescence on Hep-2 cells. ANA positivity included those with cytoplasmic and nuclear staining.

Each case was then classified as one of the following: PM, DM, IMNM, CTD-OM, IBM, CAM, ASS, non-inflammatory myopathy, unspecified myopathy and "incomplete data". This decision was made by consensus of expert opinion (HC, JBL, JLM). As part of this process, existing diagnostic/classification criteria for each subgroup were applied where available, noting that each of these patients had already been defined as an IIM case using the EULAR/ACR criteria. IBM was diagnosed if the patient was classified as clinico-pathologically defined or clinically defined IBM by 2013 ENMC criteria(4), IMNM was diagnosed according to 2018 ENMC proposed criteria(5), CTD-OM was diagnosed according to Troyanov criteria(8) and ASS was diagnosed either by Connor criteria(6) or Solomon Criteria(7). DM was diagnosed according to the presence of typical skin rash and/or presence of DM-specific abs (Mi-2, Tif1 gamma, MDA5, NXP2, SAE1). CAM was diagnosed if the patient developed a malignancy within 3 years of myositis diagnosis. Finally, PM was defined as symmetrical muscle weakness, without skin involvement and with clear response to immunosuppressive therapy (where data was available) in those that they did not fulfil other subgroup criteria.

For patients not meeting these criteria, the following labels were applied: 'Non-inflammatory myopathy' was defined as a confirmed diagnosis or strong clinical suspicion of non-inflammatory

myopathy such as limb-girdle muscle disease (LGMD), dystrophinopathy or myofibrillar myopathy made during follow-up; 'Unspecified myopathy' was diagnosed where consensus could not classify the case into one of the stated sub-groups, despite the availability of all relevant clinical information and investigation results; 'Undeterminate due to incomplete data' was used only where there was insufficient data to classify the patient due to important outstanding investigation results or clinical information.

This study was performed as part of a quality improvement project evaluating the neuromuscular service at SRFT. Case notes and other data were reviewed retrospectively without alteration to patient management. Given this context, and after consultation with the Health Research Authority (via www.hra-decisiontools.org.uk), this study proceeded without further requirement for ethical authorization.

Statistical methods

Statistical analyses were performed using SPSS version 22. Categorical numbers were presented as numbers and percentages. Continuous variables were presented as a mean and standard deviation.

RESULTS

Thirty-seven patients with PM according to EULAR/ACR IIM criteria and by expert opinion were included in the analysis. Twenty-six patients (26/37, 68.4%) were female. The mean age at diagnosis was 57 years (SD 16.25) and mean follow up was 5.2 years (SD 4.8).

After consensus discussions, nine patients (9/37, 24.3%) retained classification as PM, representing 3.5% (9/255) of the original cohort of 255 patients. The remaining 27 were reclassified as follows: CTD-OM (7/37, 18.9%), IMNM (5/37, 13.5%), CAM (3/37, 8.1%) unspecified myopathy (6/37, 16.2%), DM (2/37, 5.4%), and non-inflammatory myopathy (1/37, 2.7%, myofibrillar myopathy). Four patients (4/37, 10%) had insufficient data available to allow for a defined diagnosis.

The restricted modern entity of PM

Of the 9 patients retaining classification as PM, 6 (66.6%) were female, and mean age at diagnosis was 58.11 years (SD 13.69). Clinical characteristics are represented in Table 1. Mean CK at diagnosis was 2446.9IU/L (SD 2204). Regarding autoantibody testing, 9 patients (100%) were tested for the complete myositis autoantibody panel and 3 (33.3%) were specifically tested for the presence of HMGCR antibodies and found to be negative (table 2). EMG revealed a myopathic pattern in 5/6 (83.3%) patients tested. Muscle MRI was performed in 5 cases, which showed muscle oedema in a pattern compatible with active myositis in 3/5 (60%). None of these 9 patients had prior exposure to statins or other myotoxins.

A complete muscle biopsy report was available in 7/9 PM-classified patients (77.7%); diffuse HLA-1 upregulation was present in 4/7 patients (57.1%), endomysial inflammatory infiltrates in 4/7 (57.1%) and perimysial infiltrates in 3/7 (42.8%) (in conjunction with endomysial infiltrates in one patient). Rimmed vacuoles, protein aggregation, perifascicular atrophy and perifascicular necrosis were not present in any of the reviewed biopsy reports.

Eight out of 9 patients received treatment with glucocorticoids (88.9%). Seven (7/9, 77.7%) received treatment with concomitant immunosuppressants (5/9 methotrexate, 1/9 cyclosporine, 1/9 methotrexate and cyclosporine). Seven patients (77.8%) responded clinically to treatment, two did not have sufficient data available to confirm treatment response.

Most patients with PM could be reclassified as another IIM subgroup

The characteristics of patients who were reclassified as a non-PM IIM subgroup are summarised in Tables 1 and 2. CTD-OM patients (7/37, 18.9%) had overlap features (such as Raynaud's phenomenon, sclerodactyly or arthropathy) and CTD-specific autoantibodies (Anti-PM-Scl [n=3], anti-U1-RNP [n=1], anti-Ku [n=1]). IMNM was diagnosed based on anti-HMGCR positivity in three patients, anti-SRP in one patient, and biopsy results (necrosis and mild inflammation) in one patient which was seronegative, fulfilling ENMC proposed criteria for IMNM(5).

Two patients were reclassified as DM. Both had anti-SAE antibodies, and one of them developed a classical DM rash during follow-up (neither of those two cases had skin rash at the initial evaluation). CAM was diagnosed in three patients, all seronegative, without skin rash or overlap features, all of them with malignancy diagnosed within 3 years of myopathy diagnosis. Non-inflammatory myopathy (myofibrillar myopathy) was diagnosed in another patient according to unresponsiveness to immunosuppressive treatment and muscle biopsy results, although genetic confirmation is outstanding. Within the unspecified myositis subgroup (n=6), one patient had a suspicion of IBM (not meeting ENMC criteria), one patient had a possible eosinophilic fasciitis like-syndrome (proximal weakness and pain, possible cutaneous induration on both forearms, high CRP/ESR and myofascial involvement on both biopsy and MRI), one had a HIV associated myopathy, two patients were positive for anti-Ro52 without other CTD features, and the last patient had an acute syndrome with proximal weakness and high CRP/ESR, without evidence of muscle inflammation at the time of review (normal CPK, non-specific biopsy) that responded to corticosteroids (possible polymyalgia rheumatica or viral illness).

There were 6 patients with anti-Ro52. One patient was classified as DM (anti-SAE and anti-Ro52, typical skin rash) and three were classified as CTD-OM, presenting with overlap features including Raynaud's or arthritis and positivity for an additional MAA (one patient with anti-Ku, one patient with anti-U1-RNP). Only two patients with anti-Ro52 did not have other antibodies or recorded features suggesting CTD-OM or DM.

DISCUSSION

Despite PM being common in the 255 patients classified by EULAR/ACR criteria in our previous study(10), after carefully reviewing each case, only 9/255 (3.5%) retained the diagnosis. These patients were carefully reviewed for the presence of features occurring during the additional follow-up period suggesting an alternative diagnosis. In addition, some patients were tested for the complete MSA/MAA profile by line immunoblot assay in the meantime and their biopsies were reviewed. This highlights the importance of careful examination, complete autoantibody testing and biopsy analysis when defining IIM subgroup in clinical practice. Most of our PM cases were reclassified as either IMNM or CTD-OM. ASS and IBM were not major subgroups, likely because these patients were correctly classified as such in the original cohort(10), nevertheless, these subgroups should be considered as a differential diagnosis.

Anti-Ro52 autoantibodies have been an issue when classifying our cohort. These antibodies are associated with various CTDs, including systemic lupus erythematosus, Sjögren's syndrome, systemic sclerosis, inflammatory myopathies and autoimmune hepatitis(13–15). Within IIM patients, anti-Ro52 has been described in ASS and DM, often in association with other antibodies, with a higher risk for ILD and worse prognosis in some studies(16–18). When assessed in patients with anti-U1-RNP antibodies, anti-Ro52 has been associated with higher risk for glomerulonephritis and pericarditis(19). It is difficult to classify patients based only on anti-Ro52 presence as the autoantibody is found in several CTDs. Within IIM, anti-Ro52 is described in several subgroups and frequently associated with other MSA or MAA. Only two anti-Ro52 patients did not present with overlap features or other antibodies. Despite being tested for the complete myositis autoantibody profile, no other MAA or MSA were identified in these patients. Given the retrospective design of this study, it is possible that some CTD features were present in some of those patients but not reported.

The widespread use of Bohan and Peter criteria(1,2) has likely resulted in overestimation of the relative frequency of PM. Several studies have since reported PM is less frequent than previously thought, and even question the existence of the entity altogether(20–23). In a recent study by Mariampillai *et al*(24), 260 patients with IIM were classified into subgroups using multiple correspondence and hierarchical clustering analysis. Four clusters were defined, which corresponded to IBM, IMNM, DM and ASS. All the previous PM patients were reclassified in to one of these four subgroups, adding further evidence to suggest that PM does not represent a significant subgroup of IIM patients.

Limitations

The present study has several limitations. First, due to the retrospective design, data available for the cohort is limited in some cases. For example, complete autoantibody testing and biopsy results were not available for every patient. Consequently, some of our patients classified as PM could still belong to other subgroups, keeping in mind that some clinical features could go unnoticed and some antibodies and biopsy reports were not available. Second, the experts involved at our centre share similar interpretation of case phenotypes, but this may not be representative of IIM experts more generally, nevertheless, all the patients that were diagnosed with IBM, IMNM or OM fulfilled published diagnostic/classification criteria. Third, whilst MSA and MAA testing using line immunoblot assays has excellent sensitivity and specificity, occasional false positives do occur which could contribute to misclassification(25,26). However, we carefully reviewed the clinical details of each case in addition to the autoantibody results. We therefore did not classify cases using exclusively MSA/MAA data, reducing the chance of misclassification due to false positive/negative results.

CONCLUSION

After carefully reviewing 37 patients previously diagnosed with PM, our study confirms that PM can now be regarded as a rare IIM subgroup, with most cases reclassified as alternative disease subgroups. IMNM and CTD-OM were the main alternative diagnosis. Those retaining a diagnosis of PM were characterized by symmetric muscle weakness, without skin rash or significant CTD features, no MSA or MAA, muscle biopsies with HLA-1 upregulation and/or endomysial CD8 inflammatory infiltrates in most of the patients, and immunosuppressive treatment responsiveness.

Current classification criteria encompass a wide definition of PM, and for the most part such patients can now be clinically reclassified in other subgroups. A thorough examination, comprehensive autoantibody testing, and careful interpretation of the biopsy results is recommended to accurately classify suspected IIM cases. In the future, we think that classification criteria should include a stricter definition of PM, including differentiation with other conditions which are now regarded as different entities, such as INMN or CTD-OM.

REFERENCES

1. Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). N Engl J Med. 1975;292(7):344–7.

2. Bohan A, Peter JB. Polymyositis and dermatomyositis (second of two parts). N Engl J Med. 1975;292(8):403–7.

3. Selva-O'Callaghan A, Pinal-Fernandez I, Trallero-Araguás E, Milisenda JC, Grau-Junyent JM, Mammen AL. Classification and management of adult inflammatory myopathies. Vol. 17, The Lancet Neurology. Lancet Publishing Group; 2018. p. 816–28.

4. Rose MR, ENMC IBM Working Group. 188th ENMC International Workshop: Inclusion Body Myositis, 2-4 December 2011, Naarden, The Netherlands. Neuromuscul Disord. 2013 Dec 1;23(12):1044–55.

5. Allenbach Y, Mammen AL, Benveniste O, Stenzel W, Allenbach Y, Amato A, et al. 224th ENMC International Workshop:: Clinico-sero-pathological classification of immune-mediated necrotizing myopathies Zandvoort, The Netherlands, 14–16 October 2016. In: Neuromuscular Disorders. Elsevier Ltd; 2018. p. 87–99.

6. Connors GR, Christopher-Stine L, Oddis C V., Danoff SK. Interstitial lung disease associated with the idiopathic inflammatory myopathies: What progress has been made in the past 35 years? Vol. 138, Chest. American College of Chest Physicians; 2010. p. 1464–74.

7. Solomon J, Swigris JJ, Brown KK. Myositis-related interstitial lung disease and antisynthetase syndrome. J Bras Pneumol. 37(1):100–9.

8. Troyanov Y, Targoff IN, Tremblay JL, Goulet JR, Raymond Y, Senécal JL. Novel classification of idiopathic inflammatory myopathies based on overlap syndrome features and autoantibodies: Analysis of 100 French Canadian patients. Vol. 84, Medicine. 2005. p. 231–49.

9. Lundberg IE, Tjärnlund A, Bottai M, Werth VP, Pilkington C, Visser M de, et al. 2017 European League Against Rheumatism/American College of Rheumatology classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups. Ann Rheum Dis. 2017 Dec;76(12):1955–64.

10. Parker MJS, Oldroyd A, Roberts ME, Lilleker JB, Betteridge ZE, McHugh NJ, et al. The

performance of the European League Against Rheumatism/American College of Rheumatology idiopathic inflammatory myopathies classification criteria in an expert-defined 10 year incident cohort. Rheumatol (United Kingdom). 2019 Mar 1;58(3):468–75.

11. Zhang X, Yang X, Ji L, Zhang Z. Validation of 2017 classification criteria for adult and juvenile idiopathic inflammatory myopathies proposed by EULAR/ACR in Chinese patients. Int J Rheum Dis. 2019 Jul;22(7):1278–82.

12. Aggarwal R, Ringold S, Khanna D, Neogi T, Johnson SR, Miller A, et al. Distinctions Between Diagnostic and Classification Criteria? HHS Public Access. Arthritis Care Res. 2015;67(7):891–7.

13. Robbins A, Hentzien M, Toquet S, Didier K, Servettaz A, Pham BN, et al. Diagnostic utility of separate anti-Ro60 and anti-Ro52/TRIM21 antibody detection in autoimmune diseases. Front Immunol. 2019;10(MAR).

14. Lee AYS. A review of the role and clinical utility of anti-Ro52/TRIM21 in systemic autoimmunity. Vol. 37, Rheumatology International. Springer Verlag; 2017. p. 1323–33.

15. Wielosz E, Majdan M, Dryglewska M, Targonska-Stepniak B. Overlap syndromes in systemic sclerosis. Postep Dermatologii i Alergol. 2018 Jun 1;35(3):246–50.

16. Marie I, Hatron PY, Dominique S, Cherin P, Mouthon L, Menard JF, et al. Short-Term and Long-Term Outcome of Anti-Jo1-Positive Patients with Anti-Ro52 Antibody. Semin Arthritis Rheum. 2012 Jun;41(6):890–9.

17. Temmoku J, Sato S, Fujita Y, Asano T, Suzuki E, Kanno T, et al. Clinical significance of myositis-specific autoantibody profiles in Japanese patients with polymyositis/dermatomyositis. Medicine (Baltimore). 2019 May 1;98(20):e15578.

18. Bauhammer J, Blank N, Max R, Lorenz H-M, Wagner U, Krause D, et al. Rituximab in the Treatment of Jo1 Antibody-associated Antisynthetase Syndrome: Anti-Ro52 Positivity as a Marker for Severity and Treatment Response. J Rheumatol. 2016 Aug 1;43(8):1566–74.

19. Casal-Dominguez M, Pinal-Fernandez I, Corse AM, Paik J, Albayda J, Casciola-Rosen L, et al. Muscular and extramuscular features of myositis patients with anti-U1-RNP autoantibodies. Neurology. 2019 Mar 26;92(13):e1416–26.

20. Van der Meulen MFG, Bronner IM, Hoogendijk JE, Burger H, Van Venrooij WJ, Voskuyl

AE, et al. Polymyositis: An overdiagnosed entity. Neurology. 2003 Aug 12;61(3):316–21.

21. Amato AA, Griggs RC. Unicorns, dragons, polymyositis, and other mythological beasts. Neurology. 2003 Aug 12;61(3):288–9.

22. Chahin N, Engel AG. Correlation of muscle biopsy, clinical course, and outcome in PM and sporadic IBM. Neurology. 2008 Feb 5;70(6):418–24.

23. Senécal J, Raynauld J, Troyanov Y. Editorial: A New Classification of Adult Autoimmune Myositis. Arthritis Rheumatol. 2017 May 6;69(5):878–84.

24. Mariampillai K, Granger B, Amelin D, Guiguet M, Hachulla E, Maurier F, et al. Development of a New Classification System for Idiopathic Inflammatory Myopathies Based on Clinical Manifestations and Myositis-Specific Autoantibodies. JAMA Neurol. 2018 Dec 1;75(12):1528–37.

25. To F, Ventín-Rodríguez C, Elkhalifa S, Lilleker JB, Chinoy H. Line blot immunoassays in idiopathic inflammatory myopathies: Retrospective review of diagnostic accuracy and factors predicting true positive results. Vol. 4, BMC Rheumatology. BioMed Central; 2020.

26. Mahler M, Betteridge Z, Bentow C, Richards M, Seaman A, Chinoy H, et al. Comparison of Three Immunoassays for the Detection of Myositis Specific Antibodies. Front Immunol. 2019;10:848.

STATEMENTS

Funding

No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

Conflict of interest

There are no conflicts of interest for any author.

Ethics

This study was performed as part of a quality improvement project evaluating the neuromuscular service at SRFT. Case notes and other data were reviewed retrospectively without alteration to patient management. Given this context, and after consultation with the Health Research Authority (via www.hra-decisiontools.org.uk), this study proceeded without further requirement for ethical authorization.

Data availability

The data underlying this article are available in the article and in its online supplementary material.

Authorship criteria

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by all authors. The first draft of the manuscript was written by Jesús Loarce-Martos, James B. Lilleker and Hector Chinoy, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.